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To Examiner Smilly Bernhardt

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Figa

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Coples to Subject

Respectfully submitted,

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I-{(INDOL-3-YL)CARBONYLJPIPERAZINE DERIVATIVES

The present invertion relates to :-[(fr.do'-3-yl),carborryllpiperazine derivatives, to pharmaceutical compositions comprising the same and to the use of these 1-{(indo-3-yl)carbonyl]otperazine derivatives as cannabloold agonists in the treatment of pain and other disorders.

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1-{(Indol-3-yi)carbony|]pperazine der vativəs are known as compounds endowed with interesting pharmacological properties. 1-{(Indol-3-yi)carbony|]pperazine derivatives with unsubstituted indole nitrogen atom are disclosed in WO9806715 (SmithKlireBeecham Corp.) as anti-inflammatory agents. Related 1-{(Indol-3-yi)carbony||piperazine derivatives which may also be substituted at the indole nitrogen atom are disclosed in WO9143746 (Nippon Shinyaku Co.) as compounds having antiinflammatory and nephrotropic activities.

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15. 14(1-Benzyl-indol-3-yl)carbonyllpiperazine derivatives were disclosed in a study on H1-receptor antagonists (Battaglia, S. et al. *Eur. J. Med. Chem.* 34, 93-105, 1999) and in a study on anti-inflammatory agents (Duflos, M. et al. *Eur. J. Med. Chem.* 36, 245-553, 2001), and found to be of relatively low activity in both studies.

Recently '-{(ndol-3-y/)carbony/pperazine derivatives were generically described in WOO158839 (Bristo-Myers Squibb) as being active modulators of the cannebhold receptor and as such useful in the treatment of respiratory diseases. No specific '- 'tindol-3-y/)carbony/piperazine derivatives were disclosed in this patent application.

Pain treatment is often limited by the side effects of currently available medication.

For moderabe to severe pain, opioids are widely used. These agents are cheap and effective but suffer from serious and potentially life-threatening side-effects, most notably respiratory depression and muscle rigidity. In addition, the doses of opioids which can be administered are limited by haused, emesis, constitution, prunits and uninary retention, often resulting in patients effecting to receive sub-optimal pain control rather than suffer these distressing side affects. Furthermore, these side-effects often result in patients requiring extended hospitalisation. Opioids are Highly addictive and are scheduled drugs in many territories. There is therefore a demand for new analgesics that have an improved side effect profile compared to currently used products, at equi-aralgesic boses.

Evidence is accumulating thet can nacinal agentsts have potential as analysic and inflammatory agents. Two types of cannab nod receptors are implicated, the

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cannationid CB1 receptor, which is located primarily in the central nervous system

but which is also expressed by peripheral neurones and to a lower enternt in other per pheral tissues, and the cannabincid CB2 receptor, which is rucstry located in immune cells (Howlett, A.C. et al.: International Union of Pharmacology. XXVII. Classification of Carnabinoid Receptors Pharmacol. Rev. <u>54</u>, 161-202, 2002). While the CB2 receptor has been implicated in modulating the immune and ancimitant matory response of carnabinoids, cannabinoid receptor agonists, especially those acting at the CB1 receptor have recently been suggested as useful in the treatment of pain (Iversen, L. and Chapman, V.: Cannabinoids: a real prospect for pain raise? Outernt Opinion in Pharmacology, <u>2</u>. 50-55, 2002 and references therein). Cannabinoid receptor agonists, such as CP 55,940 and WIN 55,212-2, produce potent antinoclosoption with equivalent efficacy to morphine in animal models of acute pain, persistent inflammatory pain and neuropathic pain. The known cannabinoid agorists are in general highly libophilic and insolube in water. There is a thus a need for carnab noid agonists with improved properties for use as therepeut clears.

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o this end the present invention provides 1- (indol-3-yl)carbon//Ipiperazine derivatives having the general formula I

Formula I

wherein

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R represents 1-4 subs: ituents independently selected from H. (C;.,)alkyl (cpfionally substituted with halogen), iC;.,)alkyloxy (cpfionally subs:itu:ed with halogen), halogen, OH, NH₂, CN and NO₂;

25 R₁ is (C₅₄)cycloalkyl or (C_{5E})cycloal cenyl;

R2 is H, methyl prethy;

ેર, Rs, Rs' Fa', Rs, રેક and Rs'are independently hydrogen or (C₁₂/alkyl, optionally substituted with (C₁₂/alkylcxy, halogen or OH;

Re is hydrogen or (C...jelkyl, optionally substituted with (C...jalkyloxy, halogen or OH;

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Py forms together with R₈ a 4-7 membered seturated heterocyclic ring, optionally containing a further heteroatom selected from O and S; or R₇ is -1, (C₁₋₄)a kyl or (C₃₋₆)cyc oa kyl, the alky, graups being optionally substituted with OH, halogen or iC₁₋₄)alky oxy; or a pharmaceutically acceptable salt thereof, as agonists of the cannablooid receptor, which can therefore be used in the treatment of pain such as for example peri-operative pain, chronic pair, neuropathic pain, cancer pain and pain and spasificity associated with multiple sclerosis.

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Fe forms together with R, a 4-7 membered saturated reterocyclic ting, optionally

containing a further heteroatom selected from O and S;

The compounds of the invention are generically described in WO0158369 (supra) as cannatinoid receptor modulators for treating respiratory disease. These modulators are preferentially identified therein as CB2 modulators. The majority of compounds which are disclosed in WO0158869 are characterized by the presence of a 2-(2-1) modulatory side chain at the 1-position of an indole or indazale core structure. The 1-(Indol-3-yt)carbonyl]piparazine derivatives of the invention are distinguished from those of WO0158869 by having a cyclopentylmethyl- or a cyclohexylmethyl side chain at the corresponding position, a feature which, unite a 2-(4-norpholinyl)ethyl side chain or a benzyl side chain, provides compounds having CB1 agonist activity.

The term (C₁₋₁)alkyl as usen in the definition of formula I means a branched or unbranched elkyl group having 1-4 carbon atoms, Ike buryl, Isobutyl, tentiary butyl, probyl, isopropyl, ethyl and methyl.

15 In the term (G₁Jalkyloxy, (G₁Jalkyl has the meaning as defined above. The term (G₂J)γcloalkyl means a saturated cyclic alkyl group having 5-8 carbon axions, and can thus represent cyclopentyl, cyclohexyl, cycloheptyl or cycloocyl. Preferred (G₂J)γcloalkyl groups are cyclopentyl and cyclohexyl.

The term (C₆₋₃)cycloa kenyl means a cyclic alkeny group having 5-8 carpon atoms 30 and at least one double bond, like cyclopen;-3-enyl or cyclohax-3-enyl.
The term halogen means F, Cl, Br or

In the definition of formula I R₆ can form together with R₇ a 4-7 membered saturated helerocyclic ring, which means that R₆ together with the carbon atom to which it is bound and R₇ together with the nitrogen atom to which it is bound complete a 4-7 membered saturated ring, such as an azottoine, a pyrrolidine, a ppendine, or a 1H-azepine ing. Such rings may contain an additional O or S-heteroatom to form rings

There is a preference for 1-1(ndol-3-yl)carbonylpiperazine derivatives of formula I whereir R_2 is H and R_1 is a cyclopentyl or a cyclohexyl group.

such as a morpholine, a piperazina, a homopiperazina, an imidazolidine or a

tetrahydrothiazole ring.

whereir R₂ is H and F₁ is a cyclopentyl or a cyclohexyl group.

More prefarred are the compounds of formula (wherein in addition R represents (G₄₋₁)a kyloxy or halogen, while even more preferred are the 1-[indo-3-yl)carbonyl]-plperazine derivatives of the invertion wherein R represents a mathoxy group at the 7-position of the indole ring.

10 Especially preferred are the 1-{(ndol-3-y/)carborryllpiperazine derivatives of formula 1 wherein R₆, R₃', R₄', R₅' and R₅' are H; R₄, R₆ and R₇ are independently H or (C₁₋₄ially); or R₆ forms together with R₇ a 5- cr 3-membered saturated heterocyclic ring and R₆ is H or (C₁₋₄)alkyl.

Particular preferred CB-1 receptor agonists of the invention are:

15 1-{[1-{cycl>hexylmetl-yt}-7-ir.ethox;-1.H-indol-3-yt]parbonyl}-3,5-dimethyl-4-eff-yipiperazine;

1-{!'--(cyclohexylmethyl)-7-methoxy-1 H-indol-3-yljcarocnyl}-3,4 5-tr:methylpiperazine; (Sy1-{|T-(cyclohexylmethyl)-7-methoxy-1 H-indol-3-yljca bonyl}-3,4-dimethyl-

piperazlne;

20 (S)-2·([1-(cyclohaxylmethy/}-7-methaxy-1/H-indol-3-yljcarborryl]-octahydro-2/H-pyrido-2/H-pyridol-1,2-a]pyrazine;

(S)-2-{[1-(cyclohexylnethyl)-7-methoxy-1*H*-indol-3-yljcarbonyll-octahydro-2*H*-pyrrotc-...2-a]pyrazine; and (S)-2-{[1-(cyclopentyln:ethyl)-7-methoxy-1*H*-indol-3-yl]carbonyl}-octatydro-2*H*-pyrido-

25 [1,2-e]byrazine; or pharmaceutica ly acceptable salts thereof.

The '-[(indol-5-yl)carbony]pperazine derivatives of the Invention may be prepared by methods known in the art of organic chemistry in general. If one specifically such compounds can be prepared using procedures outlined by C. J. Swain et al. (J. Med. 30 140-151, 1991) and by P. E. Pererson, J. P. Worlf H and C. Niemann (J. Crg. Chem. 23, 303-304, 1958) or by modification of these procedures

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Formuta III

Formula II

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derivetive thereof, such as a carboxylic acic halide, preferably a choride or a -{(Indol ঔপ্যাcarbony!)piperazines of Formula I can for instance be prepared from the browids, with ϵ compound of Formula III where $R_\epsilon-R_1$ have the meaning as previously defined. When C(O)X represents a carboxylic acid (Le., X is hydroxy) the condensation of a compound of Formula II, wherein R1. R3 and R have the meaning condensation reaction can be effected with the aid of a coupling reagent, such as for example carbonyl diimidazole, dicyclohexylcarocdiimide and the like, in a solvent as previously defined and CiO)X represents a carboxylic acid or an such as dimethylicimamide or distrioromethane.

When C(O)X represents a cartroxylic acid halide (i.e., X is halide) the condensation with the amine derivative III can be carried out in the presence of a base, for example triethylamine, in a solvert such as dichloromethans. Compounds of formula III can be obtained from commercial sources, prepared by literature procedures or macifications of literature procedures grown to those วยrsons skitlad in the art. For examp e, compounds of formula III can be prepared by educton o' a diketop perazine, using a reducing agent such as lithium aluminium hycride or borane-tetrahydrofuran complex as described by M. E. Jung and J. C. Rohloff (J. Org. Chem. 30, 4909 4913, 1985). Diketoolperazines can be prepared by a variety of routes, as described by C. J. Dinsmore and D. C. Bershore (Tetrahedron 58, 3297-3312, 2002).

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Compounds of formula II can be prepared by reaction of a compound of formula IV. where R has the meaning as previously defined, and a compound of 'ormula V. for exemple a halide or an alky' sulforate, in the presence of a base such as sodium where R. and R. have the meanings as previously defined and Y.s a teaving group, hydride. The carboxylic acid can be converted to a carboxyto acic halids, if desired, for example a carboxylip apid chloride, using a reagent such as oxalyl chloride. 22 ဓ

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Formula V

Formu a ľV

Compounds of formula Vican be obtained from commercial sources, prepared by Rerature procedures or modifications of literature procedures known to those persons skilled in the art.

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For example, compounds of formula V where Y is para-toluenasulfonete can be prepared from compounds of formula V where Y is hydroxyl using a method described by B. Török et al (J. Chara. Soc. Perkin Trans. 1, 801-804, 1993). Compounds of formula V where Y is hydroxyl and R₂ is hydrogen can be prepared by reduction of a carboxylic acid or carboxylic ester, using a reducing agent such as borane-tetrahydrofuran complex or lithium aluminium hydride.

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Compounds of formula IV car be accessed from compounds of formula VI by acyation at the 3-position, using an acyating reagent. For example, compounds of formula IV can be accessed from compounds of formula VI by treatment with trifluoroacetic aryhydride in a solvent such as dimethyllormarricle, followed by hydrolysis in squeous sodium hydroxice at an elevated temperature.

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Formu

Formula VI

Formula VII

Compounds of formula VI can be obtained from commercial sources, prepared by literature procedures or modifications of Iterature procedures known to those persons skilled in the art.

Compounds of formule I can alternatively be prepared by acylation of a compound of formula VII, using an acylating reagent. For example, compounds of formula II where X is chloride can be prepared by reaction of a compound of formula VII with oxaly chloride in a solvent such as 1,1,2,2-tetrachloroethane followed by rearrangement at elevated temperature.

Compounds of formula VII can be prepared by reaction of a compound of formula VI with a compound of formula VI in the preserve of a base such a sortium hydride.

The skilled person will likewise appreciate that various 1-[(indol-3-yl)ca-bonyl]-perazine derivatives of Formula I can be obtained by appropriate conversion reactions of functional groups corresponding to certain of the substituents R and R.-R. For example, compounds of formula I wherein R, is (C₁₋₄)alcyl or (C₃₋₂)cycloalcyl, the alkyl groups of which may be substituted with OF, halogen or (C₁₋₄)alkyloxy, can be prepared by the reaction of a compound of formula, wherein Fy is hydrogen with a (C₁₋₄)a kyl relief or a functionalised (C₁₋₄)alkyl natide, in the presence of a base such as potassium carbonate.

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Compounds of formula I wherein R is (C₁₄)alkyloxy or functionalised (C₁₄)alkyloxy may be prepared by the reaction of a compound of formula I wherein R is hydroxy with a (C₁₄)alkyl halide or a functionalised (C₁₄)alkyl halide, in the presence of a base such as socium hydride.

Compcunds of formula I where I R is NH, may be prepared by the reaction of a compound of formula I wherein R is nitro with a reducing eigent such as hydrogen / palladium on activated carbon.

2C The 1-[(indcl-3-yl)carbony[piperazine derivatives of Formula I and their salts may contain at least one centre of chirality, and exist therefore as stereoisomers, including enanticmers and clastarecmens. The present invention includes the afterementioned stereoisomers within its scope and each of the inclividual R and S enanticmers of the compounds of formula I and their sats, substantially free, i.e. associated with less than 5% preferably less than 2%, in particular ess than 1% of the other enanticmer and mixtures of such enant omers in any proportions including the recemic mixtures containing substantially equal emcunis of the two enanticmers.

Methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, e.g. synthesis with chiral induction or starting from chiral of infermediates, enanticselective enzymatic conversions, separation of stereoisomers or enantioners using chromatography on chiral media. Such methods are for example described in *Chirality in Inductiny* (edited by A.N. Collins, G.N. Sheldrake and J. Crooby, 1992; John Wiley).

Pharmaceutically acceptable satts may be obtained by treating a free base of a corrogund of formula I with a minera acid such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulfuric acid, or an organic acid such as for example

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acd, gycolic acid, succinc acid, propionic acid, acetto acid, methana sufforic acid, and the like.

The compounds of the invention may exist in unsolvated as well as in solvated forme with pharmacautically acceptable solvents such as water, ethernol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purpose of the invention.

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ascorble acid, sitric acic, tarbaric acid, lactic acid, mafele acie, malonic acid, 'umaric

10 The present invention further provides pharmaceutical compositions comprising a 1[{ ndol-3-y/}] carbony||prerazine derivative raving the general formula i, or a
pharmaceutically acceptabe sat thereof, in admixture with pharmaceutically
acceptable aux laties, and optionally other therapeutic agents. The term
"acceptable" means being compatible with the other irgnedients of the corr position
15 and not deletarious to the reopients thereof. Compositions include e.g. those
suitable for oral, subingual, subcutaneous, intravenous, epidural, intrathecal,
intramuscular, transplemal, pulmonary, local, or restal actrinistration, and the like, all
in unit dosage forms for administration.

For oral administration, the active ngredient may be presented as discrete units, such as tablets, capsules, poxiders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invertion may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze driec (tyophifized) condition requiring only the addition of steriles i quid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable audillaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remington: The Scharce and Practice of Phermacy (20th Edition, Lippincott Williams & Wilkins, 2000 see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pitis, tablets, or be processed into capsules, suppositiories or patches. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, or as a spray, e.g. a nasa spray.

For making solid dosage units, the use of conventional acditives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the

lose derivatives and the like, or mixtures thereof, used in suitable amounts. For parerteral administration, aqueous suspensions, isotonic saline solutions and sterile injectables solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol. The invantion further includes a pharmaceutical composition, as nereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

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invention can be administered as soild compositions include actose, starch, cellu-

The 1-{indol-3-y}carbory/jpiperazine derivatives of the invention were found to be agorls;s of the CB-1 receptor, as determined in a human CB-1 reporter assay using CHO ce.ls. Methods to determine receptor binding as well as in vitro biological activity of cannabiating receptor modulators are well known in the art. In general expressed receptor is contacted with the compound to be tested and binding or stimulation of a functional response is measured.

To meas are a functional response Isolated DNA er coding the CB1 receptor gene, preferatly the human receptor, is expressed in suitable nest cells. Such a cell might be the Chinese Hamster Cvary cell, but other cells are also suitable. Preferably the

20 cells are of mammalian origin.

Methods to construct recombinant CB1 expressing cell I nes are well known in the ant (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor Laboratory Press. Cold Spring Harbor, latest edition). Expression of the receptor is attained by expression of the DNA encoding the desired protein. Techniques for

ligation of additional sequences and construction of autiable expression systems are all, by now, well known in the art. Portions or all of the DNA encoding the desired protein can be constructed synthetically using standard solid phase techniques, preferably to include restriction sites for ease of ligation. Suitable control elements for transcription and translation of the included coding sequence can be provided to the DNA coding acquences. As is well known, expression systems are now available

30 DNA coding sequences. As is well known, expression systems are now available with a wide variety of hosts, including prokaryotic nosts such as bacteria and eukaryotic hosts such as yeas;, plant cells, insect cells, marrinalian cells avian cells and the like.

Cells expressing the receptor are then contacted with the test compound to observe binding, or stimulation or inhibition of a functional response.

A ternal vely isolated cell membranes containing the expressed CB1 (or CB2)

receptor may be used to measure binding of compound.

be used. The most widely used radiolebelled cannabinold probe is [PHJCP=55940, which has approx mately equal affinity for CB1 and CB2 binding sites.

Another assay involves screening for cannabinoic CB1 agonist compounds by determining the second messenger response, such as for example measurment of receptor mediated changes in cAMP or MAPkinase pathways. Thus, such a method involves expression of the CB1 receptor on the cell sufface of a host cell and exposing the cell to the rest compound. The second messenger response is than measured. The level of second messenger will be reduced or increased, depending on the effect of the test compound upon binding to the receptor.

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For measurement of binding radioactively or fluorescently labeled compounds may

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In addition to direct measurement of e.g. cAMP levels in the exposed cell. cells can be used which in addition to transfection with receptor encoding DNA are also transfected with a second DNA encoding a reporter gene the expression of which correlates with receptor activation. In general, reporter gene expression of which correlates with receptor activation. In general, reporter gene expression of which correlates with response element reacting to changing levels ofsecond messenger. Suitable reporter genes are e.g. LacZ, alkalire phosphatase, frefly fubilitiense and green fluorescence protein. The principles of such transact vation assays are well known in the art and are described e.g. in Stratowa, Ch. Hinmler, A and Czernilotsky, A.P., Curr.Opin. Biotechnol. 6, 574 (1995). For selecting active agenist compounds or the CB1 receptor the ECs, value must be < 10° M, preferably < 10° M.

The exmocunds may be used in the treatment of pain such as for exempte pertoperative pain, chronic pain, neuropathic pain, cancer pain and pain and spasticity associated with multiple sclerosis.

25 Cannabinoid agenists of the invention would also potentially be useful in the treatment of other disorders including multipe aderosis, spasticity, infamination, glaucine, nausea and emesis, loss of appetite, sleep disturbances, respiratory disorders, allergies, epilepsy, migraine, cardiovascular disorders, neurodegenerative disorders, enxiety, traumatic brain injury and stroke.

30 The compounds could also be used in conjunction with other analgesic drugs such as opicids and non-sieroldal anti-Inflammatory drugs (NSAIDs), including COX-2 selective inhibitors.

The compounds of the invention may be administered for humans in a sufficient amount and for a sufficient amount of time to elieviste the symptoms. Il ustratively, daily dosage levels for humans can be in the range of 0.001-50 mg per kg body weight, preferably in a daily dosage of 0.01-20 mg per kg body weight.

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The Invention is illustrated by the following Examples.

Example 1

1-81-1 Octonexylmethyl. -7-methow-1 H-rdol-3-ylcanbonyl. 4-ethybiperazine, malaic Ŋ

mixture was stirred at room temperature for 1 h, then poured into water (200 ml). The ்o a solution of 7-methaxyincole (3.5 g, 23.8 mmol) in dimethylformamide (35 m) at PC was added triffuorcacetic antrydide (4.4 ml, 31.5 mmo) over 5 minutes. The resulting 7-methoxy-3-{(trifluoromethy)carbonyljindcle prezipitate was filtered off, washing with water and used directly in the next step.

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heated to reflux with stirring for 1.1. The mixture was cooled and weshed twice with diethyl ether. The aquecies phase was then ecidified to pH 1 using 5 M hydrochloric acid and the resulting line precip tate filtered off, washed with water and dried to The damp solid was suspended in 4 M sodium hydrox de so ution (140 mi) and efford 7-methoxyIndole-3-carbox/lic acid (3.6 g).

7-Methavylndole-3-carboxytic acid (3.0 g. 16.6 mmo.) was added portionwise to a stirred suspension of sodium hydide (60% dispersion in m.neral cil, 1.56 g. 35rrmcl) in dimethylicm amide (75 ml). After 1 h, bromomethyloycich exane (5.7 g, 32.3 mmol)

ilitered off. The crude product was recrystalised from ethyl acetate to afford 1was acced. The inxture was reated to 60°C with stirring for 1 h. The mixture was ditued with water (250 m) and washed with ethyl acetate and then diethyl ether. The squeous phase was aciditied to pH 1 using 5 M hydrochloric acid and the precipitate cyclohexylmethyl)-7-methoxyindde-3-carboxylic acid (3.75 g) as a crystalline solid. ଷ

To a solution of 1-(cyclohexylme:hyl)-7-methoxyindale-8-carboxylic acid (2.5 g, 8.8 mmot) ir THF (30 mi) was addec oxatyl chloride (4.5 g, 85.3 mmo.), dropwise with The mixture was stirred at room temperature for 18 h. The volatile compenents were evaporated under reduced pressure to afford 1-(cyclohexytmethyil)-?-melhoxyindole-3-carborry1 chloride (2.7 g) as a crystalline solid. stirring. 얺

10% (VV) methanol in dich oromethane to afford the title compound (free base) as a To 1-(c/clohexylmethy). 7-methoxyindcle-3-carocnyl.chloride (* . 9 g., 6.2 r-mal) was added a solution of Akethylpiperazine (1.35 g., 11.8 mmol) in dichloromethane (60 mlj. The nixture was stirred until the acid chloride dissolved. Triethylamine (3 ml, 21.5 mmol was acded and the solution stimed at room temperature for 16 h. The eaction mixture was washed with water (2 \times 50 ml), dried with socium sulfate and evaporated to afford an oil. This was puritied by !tash chromatography eluting with 0-8 33

of maleic setid (0.83 g. 7.15 mmd) in ether (24 ml) and methanol (4 ml). The resulting mixture was ettired for 30 minutes and the solid filtered off. The solid was recrystallised from methano /diethy/ ether to afford title compound (1:1 maleic acid saft) as a crystallised from methano /diethy/ ether to afford title compound (1:1 maleic acid saft) as a crystalline solid (2.7 g, 5.4 mmo). ¹H NIMR (4COMHz, CD₂CD) & 0.89-1.08 (2Hm), 1.12-1.25 (3H, m), 1.36 (3H, t, J.7.5), 1.56 (2H, d, J. 12.5), 1.63-1.74 (3H, m), 1.77-1.89 (1H, m) 3.22 (2H, g, J.7.5), 3.30-3.35 (4H, m), 3.55 (3H, s), 5.80-4.05 (4H, m), 4.25 (2H, d, J.7.0), 6.25 (2H, s, maleate) 6.76 (1H, d, J.7.5), 7.10 (1H, t, J.7.5), 7.26 (1H, d, J.7.5), 7.53 (1H, s); E MS: m/z = 384.2 [M+H].

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The free base mas dissolved in diethyl ether (50 mf) and filtered into a stirred solution

Example 2

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1-f[1-iCyclopenNimethyl)-7-methoxy-1*H*-incol-3-ylycarbonyl]-4-ethylpiperazine, hydrochlorice salt Cyclopentaneme:hanol p-tcl:zenesultona:e was prapared by the following method: To a solution of cyclopentaneme:hanol (2.0 g, 20.0 nmol) and pyridine (2.9 ml, 36.3 rmol); in dichloromethene (20 rnl) was added p-toluenesu tonyl chloride (3.46 g, 18.1 mmol). The mixture was stirred at room tamperature for 24 h under nitrogen. The resulting mixture was washed with 2N hydrochloric acid and the aqueous keyer separated and extracted with cichloromethane. The combined organics were cried over sodium sulphate and concentrated under reduced pressure to yield cyclopenianemethanol p-toluenesulfonate as a colourless oil (4.3 g, 17.0 mmol).

cover sodium sulphate and concentrated under reduced pressure to yield cyclogentanemethanol p-tol.enssulfonate as a colourless of (4.3 g. 17.0 mmol).

The title compound was prepared following the methon of Example 1. using cyclopentanemethanol p-toluenesul onate instead of promocraethyloydorexane. 'H

NIV R (400M-12, CD₃CD) 5_H 1.29-1.25 (2H, m), 1.33 (3-, t, J7.5), 1.52-1.71 (6H, m),

25 2.39-2.49 (1-4, m), 3.24 (2H, c, J7.5), 3.05-3.35 (2H, br m), 8.35-3.70 (4-t, br m),

3.95 (3H, s), 4.38 (2H, d, J7.5), 4.40-4.65 (2H, br m), 6.79 (1H, d, J7.5), 7.10 (1H, t, J7.5), 7.27 (1H, d, J7.5), 7.60 (1H, s), EIMS: m/z = 370.2 [M+H]*.

Example 3

35 The procedure described under Examples 1 and 2 was further used to prepare the following compounds:

34: 1-if1-(c/c)ohapt/meth/f)-7-methoxy-1/H-indol-3-ylkartonyl}-4-ethylolperazine,

<u>hydrochforide saft</u> was prepared using cycloheptar.emethanol p-tol Jenesulfonate.

EIMS: m(z = 398.2 [M+H]

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38: 1-III1-(Cyclooctylmethyl)-7-mathcyy-1H-indol-3-ylcarboryll-4-e-hybiperazine, indrochlorida salf was prepared using cyclooctanemethanci p-tolusmesuffonato EINIS: m/z = 412.4 [M+H].

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3C: 1-[[1-(Cyclohexylmethyl]-7-methoxy-1H-Incol-3-//]carbonyl]-4-(2-

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hycroxyathy)piperazine, trifluoroacetic acid selt, was prepered folkwing the method of Example 1, using 1-(2-hydroxyethy))piperazine instead of A-ethypiperazine. EMS: m/z = 4C0.2 [A/-H]*.

3D: 1-111-(Cyclchexylmethyl)-7-methoxy-1H-indox-3-y learbonyl-4-(2-

methoxyethylipiperazine, tiffuoroacetic acid sat was prepared using 1-(2-10 methoxyethylipiperazine, EIMS: m/z = 414.2 [V+H]*.

3E: 1-[11-(Cyclahexy methyl)-7-methyl-1*Hin*col-3-yl]artonyl-4-ethyloperazine was obtained tollowing the method of Example 1, using 7-methy incole instead of 7-methoxyindole. EtMS: mz = 388.0 [M++]*.

3F: 1-{[1-iOxclohexvirrethyli-7-efhyl-1 H-indol-3-v][carbony]-4-ethylipe:azine was obtained from 7-ethylindole. EINS: mtz = 382.2 [M+H]*.

Example 4

1-{[1-iCyclohexylmethyl]-5-fluoro-1 //-infol-3-yl|carbonyl]-4-e:hylpiperazine, hydrochloride salt

To a solution of 5-fluoro indole (1.0 g, 7.4 mmcl) in dimethyl formamide (20 ml) was added sodium hydride (60% dispersion in mineral oil; 327 mg, 8.14 mmol). The mixture was stirred at room temperature for 10 minutes before the addition of bromomethyloyclohexane (1.3 ml 9.3 mmol). The resulting mixture was stirred at room temperature for 15 hours. A further addition of sodium hydride (170 mg, 4.23 mmol), then promomethyloyclohexane (0.65 ml, 4.65 mmol) was made and the reaction sirred for a further 15 hours.

The reaction was quenched with 2-propanol (10 ml) and then concentrated. The resulting brown gum was partitioned between ethyl acetate (50 ml) and 5% sodium hydrogen carochate solution (50 ml). The organic layer was washed with water (50 m), dried over sodium suitate and concentrated. The crude infermediate was then purified by flash of romatograp by using 95% dichloromethane, 5% methanol as eluent, to a ford 1-(cyclohexylmethyl)-5-fluoroindole (1.25g, 5.45 mmol).

To a solution of 1-(cyclohexylmethyli-5-fluorondole (208mg, 0.5 mmot) in 1,12,2-efrachloroethane (15 m) at 0°C, was added oxalyl chloride (0.122 ml, 0.945 mmol) with stirring under a stream of nitrogen. The mixure was allowed to warm to room temperature over 1 hour, then reated to 120°C for a further 1.5 nours. The mixture

hours and then partitioned between 0.4 M sodium hydroxide so ution (10 ml) and For 15 Stirring was continued for a further 10 minutes before the addition of Methylptiped chicromethane (10ml). The organic layer was washed with water (10 ml), dried over NasSO4 and concentrated. The resulting brown oil was purified by flash chromatoas eluent to yied the azine (0.125ml, 0.99mmol). The mixture was stirred at room temperature graphy using 95% dichlorcrathane, 5% methanol compound as the free base.

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wes cooled to room temperature and triethylamine (0.138ml, 0.99mmol) was added.

Hydrochlaride sell formation was achieved by the addition of hydrogen chloride 2M solution in diethyl ether (3 mf) to a solut on of the free case in diethyl ether (5 ml). The precipitate was littered and orled. The solid was crystallised from diethyl etner and methanol to afford title compound (1:1 hydrocitoric acle salt) as a crystalline solid (0.172 g, 0.42 mmol). 14 NMR (400MHz, CD₃OD) 8s 0.98-1.27 (2-1, mj, 1.17-1.27 (3H, m), 1.39 (3H, 1, J 7.5), 1.59 (2H, d, J 13.0), 1.64-1.77 (3H, m), 1.89-1.83 (1H, 1T), 3.08-3.20 (2H, 11), 2.24-3.32 (2H, 11), 3.51 (2H, 1; 1) 12.5), 3.63 (2H, 0, 1) 11.0), 4.07 (2H, d, J7.5), 4.58 (2H, d J 12.5), 7.04 (1H, 1d, J 9.0, 2.5) 7.45 (1H, dc, /9.5, 2.5), 7.47-7.51 (1H, mj, 7.77 (1H, s); E MS: miz = 372.0 [MHH] Ģ

Example 5

The procedure described uncer Example 4 was further used to prepare the following compounds: ຄ

5B: 1-{[1-(Cyclohexytmethyl)-7-fluoro-1h-indol-3-y]:carbo-ryl--4-ethylciperazine, 5A: 1-III: (Cydohexylmethyl)-6-fluoro-1.H-ndol-3-yllcarbom/l-4-ethylciperazine hyd:ochloride sal: was obtained from 6-fluorchdole. EIMS mtz = 372.0 [M+H]*

5C: 1-[[6-Bro-no-1-icyclohexylmethyl]-1H-indol-3-v||carocnyl]-4-ethylpiperazine <u>"ydroch orige salt</u> was obta ned from 6-bromoindole. EIMS; m/z = 432,4 [M+H]* 5D: 1-[[7-Bromo-t-(cyclohexy/methyl)-1/f-indol-3-yllcarbonyll-4-ethylpiperazine hydrochloride salt was obtained from 7-bromoindale. EIMS: mz = 452.5 [M-4]* hydrochlotide sal: was obtained from 7-fluoroindole. EIMS: m/z = 372.0 [M4H]* 33

5E: 1-415-C doro-1-(cyclohexv/methyl)-∴Hadcl-3-yllcarbonyl)-4-elhylpiperazire. 5F: 1-I(6-Chloro-*-(cyclohexymethyli-1/H-indxl-3-yilcarbonyl)-4-ethybjoerazine, 5G: 1-[[7-Chloro-1-icyclohexvimethyl]-1 H-indol-3-yllcarbonyl]-4-eithylpiperazine hydrochloride sall was obtained from 5-chlorohdole. EIMS: m/z = 396.2 [M+H]⁻ hydrochloride sall was obtained from 6-ch oroindole. EIMS: $m/z = 399.5 \text{ PM+H}]^-$ <u> wdrochlorida sali</u> was obtaired from 7-chloroindola. EIMS: m/z = 338.0 [M+H]⁻

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5H: 1-il3-Cvano-1-(crclohexylmethyl)-1H-indol-3-yllcerbonyll-4-ethyloiperazine

The product obtained in Example 51 was subjected to chira. HPLC separation on a Chirace OD column (2 cm x 25 cm), eluting with schewane/isopropand 96/5 (v/x) at 20 m/min flow rate. The products were cetected using a UV detector at a wavelength of 240nm.

10 <u>{-}-51: Erentioner 1</u>; retentfon time 8.1 minutes; enantfomeric excess >98% $[a]_0^{22}$ -12° (c=1.25 rng/ml n CHCt₃).

(4)-31: Enantiomer 2 retention time 1.1.1 minutes; enantion eric excess > 98%, $[a]_0^{22} + 7^{\circ}$ (c=1.50 mg/ml in CHCl₃).

5<u>J: 1-f[1-(1-Cyclohex/dethyl)-6-methoxy-1*H*-indoh-3-yltrarbonyl)-4-ethylpiperazine, tydrochloride salf, was obtained from 6-methoxylndale and 1-cyclohexy -1-p-toluenesulforyl ethane. ElMS: m/z = 398.2 [M+H⁻¹.</u>

5K: 1-[[1-(1-C/colonaxylethyl)-7-methoxy-17-Hindol-3-ylicarbonyl)-4-ethybiperazine, hydrochloride salt was obtained from 7-methoxyindole and 1-cyclohexyi-1-p-toluenesulfonyl ethane. E MS: m/z = 598.2 [M+H]*.

20 <u>51.: 1-[11-(Cyckhexylmethyl)-6-n.tro-1*H*-indol-3-yl]carbonyl}-4-ethylpiperazine, hydrochloride salt was obtained from 6-n troindole. EIMS: m/z = 399.2 [M+H]*.

5M: --[1-iCyclohexylmethyl]-7-nitro-1*H*-indol-S-yl carbonyl}-4-ethylpiperazine, hydrochloride salt was obtained from 7-nitroindole. EIMS: m/z = 399.2 [M+H]*

5N: 1-[17-Berzyloxy-1-(cyclonexylmethyl)-1*H*-Indol-3-ylicarbonyl;-4-ethylpiperazine,</u>

25 <u>Inctrochbrida salt</u> was obtained from 7-benzyloxylndola. EIMS: m/z = 460.4 [M+H]⁻.

50: 1-f 1-(Cyz'ohexylme:hyl)-6-methoxy-1-f-ndol-3-4/bgrbonyl-4-ethylpiparazina,
ma'eic acid salt was obtained from 6-methoxyindore. EIMS: m/z = 32×.5 [M+H]⁺.

5P: 1-[11-(Cyckhexylmethyl)-7-methoxy-1-f-inctrochyl-4-

isopropylpiperazine, hydroch oride salt was obtained from 7-methoxy1ndole and 1-80 isopropylpiperazine. EIMS: m/z = 398.2 [M+H]*.

50: 1-[11-(Cyclohex-3-enylmethy)-7-methoxy-1H-indol-3-y/karbonyi-4-e.hy/piperazine was obtained from 7-methoxyindole and cyclot ex-3-enemethanol p-toluenes.Jifonate. EIMS: m/z = 392.2 [M+H]*.

5S: 1-(1-(Cysloheav)meth/A)-5-fluoro-1*H*-trdol-3-ylloarbonyll-4-methylpiperazine, hydrochloride sett was obtained using 5-fluoroindole and M-methyl piperazino. EIMS: m/z = 358.2 [M4H]*.

5T: 1-{[1-(Cyclohexylmethyl)-6-flucre-1.H-indol-3-ylcarbonyl}-4-methylpperazine. hydrochloride selt was obtained from 6-fluorcindol-9 and N-methyl piperazine. EIMS: m/z = 358.0 [M+H]*.

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6U: 1-{ij.{Cyclohexylmethyl}-7-fluono-1.H-indo:3-yl carbonyl-4-methylpiperazine, hydrochloride salt was obtained from 7-fluordindole and N-methyl piperazine. Ethys: rvz = \$58.0 [M.H.]!.

10 <u>5V: 1-4[6-Chloro-1-fcvclohex/dir ethyl)-1 H-indol-3-yllcarbonyll-4-methylciperazine.</u>

<u>fxydroch/orize sall</u> was obtained from 6-chloroir.do/e and *N*-methyl piperazine. EIMS:

n/z = 374.0 [M+H]^{*}.

5W: 1-[[2-Ch oro-1-(cyclohexvlmethyl)-1/H-tdo-3-v/.carbonyl)-4-methylpiperazine. EtyS: bydroch oride sell was obtained from 7-chloroirdo e and N-methyl piperazine. Ety/S: m/z = 374.2 [W+H]*.

5X: 1-{16-Cyano-1-(cyclohexylmetty)}-1 H-indok-3-yl]carboryl}-4-methylpiperazine, hydrochloride salt was obtained from 6-cyanoincole and M-methylpiperazine. EIVIS: m/2 = 365.0 [M+H]*.

5Y: 1-[I1-(1-Cyclohexylethyl)-5-methoxy-1*H*-indok-3-y |carbonyl)-4-methyloiperaz ne, hydrochloride sail was obtained from 6-methoxyindole, *N*-methyloiperazina and 1-cyclohexyl-1-p-toluenesulfonyl ethane EIMS: m/z = 384.2 [M-H]*.

5Z: 1-[I1-(1-Cyclohexylpropyl)-1*H*-indol-3-yl|carbonyl]-4-methyloiperazine, hydrochloride sait was obtained from indole, *N*-methyloiperazine and 1-cyclohexyl-1-c-boluenesulfonyl propane. EIMS: m/z = 368.0 [M+H]*.

XI

Example 6

1-{[7-Amino-1-(evdohexylmethyl)-1/4-indol-3-y|carbonyl}-1-ethylpiperazine (200 mg. 0.5 mmol) was clssolved in methanol (10ml) to which was added palladium (5 wt. % on activated carbor; 50mg, cat.) as a stury in methanol (3ml). The system was then seeled and flushed with nitrogen before fixing a hydrogen source (calloon). The mixture was stirred a: room temperature under hydrogen for 15 hours after which it was filtered through celite and concentrated. The resulting brown oil was purified by flash chromatography using 95% dichloromethane, 5% methanol as eluent to yield the title product as the free base. "H NMR (400MHz, CO₂OD) & 0.97-1.08 (2H, m), 1.12 (3H, t, J.7.5), 1.17-1.26 (3H, m), 1.55 (2H, d, J.12.5), 1.63-1.75 (3H, r), 1.87-1.98 (1H, m), 2.44-2.55 (6H, m), 3.57 (4H, t, J.5.0), 4.20 (2H, d, J.7.5), 6.59 (1H, dd.

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J7.5; 1.0), 6.93 (1Н , 1, J7.5), 7.05 (1Н, dd, J8.0, 1.0), 7.39 (1Н, sj; EIMS: m.z 389.0 [k/+H]*.

Example 7

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1-[1-(Cyclothexy.methyl)-7-hydroxy-1*H*-Incol-3-/(Icarbony 1-4-ethylpiperazine, hydrochlaride salt

To a solution of 4-{[7-barzylaxy-1-(cyclohexytmethyl]-1/H-indole-3-yl]carbanyl}-1-ethytciperazine (1 g 2.2 mmol) in ethanol (50m), was added paliadium (5 wt. % on activated carbon; 100 mg). The mixture was hydrogenated under a pressure of 5.5 bar at 60°C for 16 hours. The resulting mixture was filtered through dicalite, and the filtrate ocnoentrated under reduced pressure to afford the title compound (free base) as a gum (865 mg, 2.3mmol).

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Hydrochlaride sail formation was achieved by the addition of hydrogen chloride (2th solution in delity) either, Sml; to a solution of the free base (180 mg, 0.5mmd); in diethyl either (5 ml). The precipitate was filtered and dried. The solid was crystallised from diethyl ether and ethand to afford the title compound (1:1 hydrochloric acid salt) as a crystalline solid (132 mg, 0.3 mmol). 1 NMR (400MHz, CD₃OD) &₁₁ 1.05 (2H, m), 1.18 (3H, m), 1.38 (3H, t, J.7.5), 1.57 (2H, m), 1.69 (3H, m), 1.92 (1H, m), 3.13 (2H, m), 3.27 (2H, q, J.7.5), 3.45 (2H, m) 3.61 (2H, d, J.1.0), 4.29 (2H, d, J.7.0), 7.52 (1H, s); EIMS: m/z = 370.2 [M+H]*.

Example 8

1-![1-(Oyclahexdir ethyt)-7-f2-fluoroethoxy}-1/4-hdol-3-y]:arbony.1-4-ethytpiperaz ne eluent to afford the title compound (54 mg, 0.1 mms),. ¹H NMR (400MHz, CD₈CD) $\delta_{\rm H}$ was purified by flash chromatography using 95% dichloromethane, 5% methanic as The resulting prown gum was partitioned between dichloromethane (50 ml) and 5% 1.C5 (2H, n), 1.19 (3H, m), 1.39 (3H, t, J.T.5), 1.56 (2H, m), 1.69 (3H m), 1.92 (1H, water (50 ml), dried ever sedium suffate and concentrated. The crude intermediate 0.54 mmol) in d'methylio: mamide (5.n.). After 30 mhutes, 1-bromo-2-fluorcefhane (49 µl, 0.65 mmol) was adoed. The mixture was heated to 60°C with stirring for 48 hours. The reaction was quenched with 2-propanal (10 mt) and then concentrated. cyclohexylmethyl)-7-hydroxy-1*H*-fr.do.e-3-yl]carbonyl}-1-ethylpiperazins (200 mg, sodium hydrogen cart onate solution (50 ml). The organic layer was washed with Sodium hycride (60% dispersion in mineral oil, 55 mg, 1.52 mmcl) was added portionwise with starting under a stream of nitrogen to a solution of 4-4;1ß ස 33

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m), 2.48 (2H, q, J7.0), 2.53 (4H, m), 3.75 (4F, 1, J5.0), 4.26 (2H, d, J7.5), 4.32 (1H, m), 4.39 (1H, m), 4.75 (1F, m), 4.87 (1H, m), 6.73 (1H, d, J8.0), 7.06 (1H, 1, J8.0), 7.26 (1H, d, J8.0), 7.44 (1H, s); EIMS: m/z = 416.2 (M+H)*.

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Example 9

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1-(11-(Cyclohexymethyli-7-etf.oxy-11-indol-3-ylcarocnyl)-4-ethylpigerazine was prepared following the procedure described under example 8, using bromosthane instead of 1-bromo-2-flucinethane. EffXS: miz = 398.2 [M+H]*.

10 Example 10

1-(11-: Oxclohexylmethyli-7-metroxy-1/H-indol-3-yllcarbaryll-2,3,5,6-

letramethy piperazine, wdrcchloride sall

To a solution of disoprocylethylamine (0.82 ml, 4.90 mmol) and 2.3,5,6-fetramethy piperazine (0.35 g, 2.45 mmol) in dichlercmethane (5 ml) was added a so ution of 1-(cyclohexylmethyl)-7-methoxyimcole-3-carbonyl chloride (0.33 g, 1.09 mmol, prepared following the melthod in Example 1) in dichloromethane (5 ml). The mixure was stirred at room temperature for 8 h, evaporated under reduced pressure and the residue purified by flash chromatography eluting with 5-10 % (v/v) methanol in dichloromethane to afford the 11.6 compound (free base) as a colourless oil (0.43).

dropwise with 2 M hydrochloric acid in diethyl either (0.3 ml) and diethyl either (3 ml), treeted dropwise with 2 M hydrochloric acid in diethyl either (0.3 ml) and diethyl either (3 ml).

The resulting precipitate was collected by filtration, weshed with diethyl either (15 ml) and dried under reduced pressure to afford the title compound (1:f hydrochloric acid satt) as a white solid (0.09 g, 0.20 mmo). The NMR (400MHz, CD₃OD) & 0.39-1.39

25 (8H m), 1.42 (6+, d, J7.0), 1.64-1.89 (9H, m), 3.44-5.70 (3H, m), 3.95 (3+, s), 4.21-4.34 (3H, m), 6.77 (1H, d, J7.7), 7.11 (1H, 1, J6.2), 7.38 (1H, d, J8.2), 7.58 (1H, s);

Example 11

EIMS: n/2 412.4 [NI4H]*.

30 1-[[1-(Cyclohexylmethyl)-7-methoxy-1H4ndol-3-yllca:bonyl:-2,5-cimethy piperazine, hydrochloride salt

—{[1-(Cyclohexylmethyl)-7-methoxy-1H-hdol-5-yl]carbo nyf.-3,5-cimathyplperazine-1-carboxy is acid terf-buryl ester was prepared following the method in Example 10 using 3,5-cimathypiperazine-1-carboxylic acid terf-buryl ester (E. J. Jacobsen et af, J. Med. Chem. 42, 1123-1144, 1999) inscead of 2,3,5,5-teramethylpiperazine. To an ice coded solution of 4-{[1-(cyclohexylmethyl)-7-methoxy-1H-indol-3-yl]carbornyl-3,5-dimethylpiperazine-1-carboxylic acid terf-buryl ester (C.52 g, 1.08 mmol) in

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dichloromethane (5 ml) was added dropwise trifluoroacetic acid (2 ml). The mixure

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The combined organic layers were the ed with magnesium suffate and evaporated to 3.95 (2H, s), 4.26 (2H, d, J 7.0), 4.74-4.86 (2H, mj, 6.75 (1H, d, J 7.5), 7.09 (*H, t, J on!. This was purified by fash chroma:ograpty داعلتام with ق-10 % (الملا) methanol المادة 3.31 mmclj. ¹H VMR (400MHz, CD₃OD) &, 1.04 (2⊣, br q, J9.0), *.11-1 25 (3H, m). socium hydroxide solution (10 ml) and extracted into dichtoromethane (2 x 30 ml). hydrochloric acid in clethyl ether (1 ml). The resulting precipitate was collected by afford the title compound (1:1 hydrochloric acid salt) as a colourless sold (0.13 g, mas allowed to warm to room temperature over 2 h before removal of any volatile .44 (6H, d, J7.C), 1.54 (2H, br d, J13.D), 1.62-1.90 (4H, mi, 3.33-3.42 (4H, m), iltration, washed with diethyl ether (15 ml) and dried under reduced pressure to components under reduced pressure. The residue was then suspended in 5 M In dichlorome:hane to afford the title compound (free base) as a colcurlass oil. ree base was dissalved in diethyl ether (3 ml) and treated dropwise with 2 M 8.0), 7.21 (1H, d, J7.5), 7.46 (1H s); EIMS: 1\(\mu\z\) 384.2 [M-+1]*.

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Example 12

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1-111-iCyclohexy/methy/1-7-methoxy-1 H-indol-3-yl carbonyl 1-3,5-3 methylciperazine hydrochloride sall

0.87 mmd, prepared following the method in Example 1) and 2.6-dimethylpiperazine dichloromethane to afford the tille compound (free base) as a colourless oll. The free (0.16 ml, 1.05 mmol) and 1-hydroxycenzotriazola (0.01 g. 0.09 mmo). The mixtures was stirred at room terr perature for 18 h. The mixture was washed with 5 M sodium 1.36 (24, br d, J '2.0), 1.62-1.90 (4H, m), 3.06 (2H dd, J '4.5, 11.5), 3.39–3.53 (2H (0.12 g, 1.05 mmolj in dichloromether.e (10 ml) was added di sopropylcarbodiimide mj, 395 (3H, s), 426 (2H, d, J7.5), 4.52 (2H, br d, J13.5), 6.77 (1H, c, J7.5), 7.1 hydroxide (2 x 10 ml), cried with magnesium sulfate and evaporated. The residue hydrochloric acid in diethyl ether (1 ml). The resulting precipitate was collected by efford the little compound (1:1 hydrochtoric acid salt) as a colcurless solid (0.15 g. To a solution of 1-(cyclo asylmethy)-7-methoxy-indole-3-carboxylic acid (0.25 g. base (0.15 g) was dissolved in defry! ether (3 mi) and treated dropwise with 2 M 6.36 mmo), 14 NNR (43CMHz CD3OD) 8,4 0.98-1.26 (5H, m) 1.32 (6H, d, J.6.5), filtration, washed with dethyl ether (15 m) and dried under reduced pressure to was purified by flash chromatography eluting with 5-10 % (viv.) methanol in (1H, ;, JB.0), 7.24 (1H, d, JB.C), 7.54 (1H, s); EIMS: m/z 384.2 [M++-]* 20 K 8

Example 13

The procedure described under example 12 was further used to prepare the following compounds

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13A: 1-[11-(Cyclohexylmethyl)-7-methoxy-1H-indoh-3-y carbonyl-3-methylpiperazine. carboxylic scid and rep-2-methylpiperazine. 1H NMR (400MHz, CD,CD) 8, 0.98-1.24 (6H, m), 1.32 (3H, d, J.6.5), 1.56 (2H, br.d, J12.5), 1.63-1.86 (4H, m), 3.17-8.22 (2H, m), 3.39-3.51 (3H, m), 3.54 (3H, s), 4.26 (2H, d, J7.0), 4.43 (2H, br d. J14.3), 6.76 (1H. d, J7.5), 7.1 (1H, t, J7.5), 7.25 (1H, d, J8.0), 7.54 (1H, s). EIMS; m/z = 370.2 hydrochloride sat was prepared using 1-(cyclohexymethyl)-7-rrethoxy-indo/e-3-S 9

Cinethy programs, hydroch oride sall was prepared using 1 (cyclopenty) methyl)-7methoxy-indole-3-zarboxylic acid and 2,6-dimethy/piperazine. 14 NMR (400MHz 13B: 1-{[1-(Cyclcrentylr-ethyl)-7-methoxy-1.h-ndol-3-yllcarboryl)-3.5-

dd, J14.5, 11.£), 3.39–3.53 (2H, m), 3.95 (3H, s), 4.37 (2H, d, J7.5), 4.52 (2H, d, J CD₃OS) δ₁ 1.24-1 36 (8H, m), 1.51-1.72 (3H, m), 2.43 (1H, heptat, J.7.5), 3.07 (2H, 14.C), 6.77 (1H; d, J.7.5), 7.10 (1H, t, J.7.5), 7.24 (1H, d, J.8.0), 7.55 (1H, s). EIMS; m2 = 370.2 [N+H]*. 5

13C: (S)-1-[(1-(C/cloparth/methyl)-7-methoxy-1H-indol-3-yl]cart-onyl+3-

dd, J 14.5, 10.9), 3.36–9 5 (3H, m), 3.95 (3H, s), 4.37 (2H, d, J 7.5), 4.43 (2H, br d, J OD₃OD) & 1.26-* 36 (EH. m), 1.51-1.72 (6H, m), 2.42 (1H, heptet, J.7.7), 3.20 (2H, 14.5); 6.77 (114, d. J7.6); 7.10 (114, t. J7.7); 7.25 (114, d. J8.1); 7.59 (114, s). EIMS; meth/piperazire. hydrochloride salt was prepared using 1-(cyclopentylmethy)-7nethoxy-indole-3-carbcxyt cacid and (S)-2-methy piperazine. 1- NMR (400MHz, X

mz = 356.2 [M+H]* 3

00,00j &, 1.10-1.22 (5H, m), 1.38 (6H, s), *.54-1.86 (6H, m), 3.31-3.34 (2H, m), 3.2 dimet whiperazine, hydrochloride salt was prepared using 1-(cyclohexylmethyl)-?methoxy-irdo e-3-carboxylic acid and 2,2-dimethylpiperazine. H NMR (400MHz, 130: 1-[[1-(Cyc'ohexyl'nethyl)-7-methoxy-1H4ndol-3-yllcarbonyl-3,3-

(2H, dd, J14.5, 10.9), 3.81 (2H, s), 3.95 (3H, s), 3.95-2.99 (2H, m), 4.26 (2H, d. J

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7.1), 6.76 (1H, d, J7.5), 7.10 (1H, t, J.8.1), 7.24 (1H, d, J.8.0), 7.53 (1H, s). EIMS;

13E: (S)::-{[1-iCyclohexylmet.nd]-7-methoxy:1 h-ndol-3-v]]caroonyl}-3-methylm/z = 384.5 [M+H]".

indole-3-carboxylic acid and (S)-2-methylp perazine. ¹H NM:4 (400MHz, CD₆OD) 6_H <u>piperazine, hydrochloride sali</u> was prepared using 1-(cyclohexylmethyl)-7-methoxy-.G.*123 (5H, m), 1.33 (3+, d. J&5), 1.52-1.97 (6H, m), 3.16-3.27 (2+, m), 3.38-

3.51 (3H, m), 3.95 (3H, s), 4.27 (2H, d, J.7.0), 4.43 (2H, br. d, J.14.3), 6.76 (1H, d, J. 7.8), 7.10 (1H, t, J.7.9), 7.25 (1.H. d, J.8.0), 7.54 (1H, s) ElMS; m/2 = 370.0 [M4+H]².

13F: (Ri-1-[I1-(Cyclohexylmethyl)-7-methoxy-1H4ndol-3-ylcarbonyl-3-greened using 1-(cyclohexylmethyl)-7-greened using 1-(cyc

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10 Example 14

:-[[1-(Cydonexylmethyl)-2-methoxy-1H-indoh3-yl/carbonyl-3,5-dimethyl-4ethylpperazina, hydrochloride salt To a solution of 1-[11-(Cyclohexylmethyl)-7-methoxy-1*H*-indo+8-y]carbony;}-3,5-dimethylpticazine (0.7 g, 1.83 mm.) and potassium carbonate (0.3 g, 2.19 mm.) in dimethylpticazine (0.7 g, 1.83 mm.) are dimethylpticazine (0.7 m, 2.10 mmol). The mixture was heated to 50°C for 18 h and ditated with water (20 ml). The suspension was then extracted with methyl terfebulyl ether (2 x 30 ml), the combined organic layers washed with water (3 x 20 ml), dried with magnesium sulfate and evaporated. The resistue was purified by flash chromatography eluting with 5-10 % (vx) methanic in direction and produced in the string complexity.

dict-foromethane to afforc the title compound (free base) as a colour ess of. The free base (0.42 g) was dissolved in diethyl ether (10 ml) and treated dropwise with 2 l/hydrochloric acid in diethyl ether (1 ml). The resulting precipitate was collected by filtration, washed with diethyl ether (15 ml) and dried under reduced pressure to afford the title compound (1:1 hydrochloric acid sall) as a white solid (0.35 g, 0.78 mmol). ¹H NIMR (4C0MHz, CD₃OD) & 0.98-1.23 (5H, m), 1.30 (5H, t, J 7.0), 1.39 (6H, d, J 7.0), 4.55 (2H, m), 3.42-3.35 (2H, m), 3.42-3.61 (4H, m), 3.95 (3H, s), 4.26 (2H, d, J 7.0), 4.55 (2H, br d, J 13.0), 6.77 (1H, d, J 8.0), 7.10 (1H, t, J 8.0), 7.27 (1H, d, J 8.0), 7.57 (1H, s). ElMS: m/z 412.4 [M+H].

30 Example 15

The procedure cescribed under example 14 was further used to prepare the following compounds:

15A: 1.f1-iOxclopentylmathyl)-7-mathoxy-1H4indol-3-ylcarbonyll-3.5-dimethyl-4ethylpiperazine, hydrochloride salt was prepared using 1-f.1-(cyclopentylmethyl)-7-35 methoxy-1H-indol-5-yl carbonyll-3,5-dimethylpiperazine, ¹H NMF (430l/Hz, CD₂OD) 5- 1.27-1.40 (5H, rr.), :.39 (6H, d, J.6.5), 1.73-1.43 (6H, m), 2.44 (1H, heptel, J.7.C),

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J14.5), 6.77 (1H, d, J8.0), 7.10 (1H, t, J8.0), 7.27 (1H, d, J8.0), 7.61 (1H, s). EIMS; rr/z = 398.0 [M4H]¹.

15B: 1-[1-Gyclohexylmethyl]-7-methoxy-1H-Indol-3-yllcatbonyl-4-athyl-2.3.5.6-letramethypicerazine, hydrochlorida sall mas prepared using 1-[1-(cyclohexyl-methypicerazine, hydrochlorida sall mas prepared using 1-[1-(cyclohexyl-methypi-7-methoxy-1H-indol-3-yllcarbonyl)-2.3.5.6-letramethypicerazine. 'H NMR (400MHz, CD₃OD) & C. 39-1.29 (8H, m), 1.32 (3H, t, J6.3), 1.44-1.88 (15H, m), 3.32-3.83 (5H, m), 3.95 (5H, s), 4.20-4.41 (3H. m), 6.77 (1H, d, J8.0), 7.11 (1H, t, J8.0), 7.37 (1H, c, J8.5), 7.55 (1H, s). EIMS; n/z = 440.2 [M+H]².

S

3.22-3.33 (2H, m), 5.42-3.61 (4H, m), 3.55 (3H, s), 4.38 (2H, d, J7.0), 4.53 (2H, brd,

15C: 1-i[1-(Cyclohexylmethyl)-7-methoxy-1/H-hdcl-3-yllcarbonyl)-2,6-dimethyl-4-ethylpiparazing, hydrochloride salt was prepared using 1-i[1-(cyclohexylmethyl)-7-methoxy-1/H-indol-3-yllcarboryl]-2,6-dimethylpiperazine 1-i NMR (40CMHz, CD₃OD) δ_h 0.37-1.22 (5-1, m), 1.43 (3H, 1, J.7.0) 1.45 (6H, d, J.8.0), 1.51-1.88 (6H, m), 3.23-3.41 (4H, π), 3.55 (2H, br c, J·1.0), 3.95 (3H, s), 4.26 (2H, d, J.7.0), 4.88 (2H, br s), 1.51-1.88 (1H, 3, J·7.5), 7.1 (1P, ε, J.8.0), 7.23 (1H, c, J.8.0), 7.48 (1H, s), Εlt/S; π/z = 4.24 [M+H⁺*.

15 6.78 (1H, 3, 47.5), 7.1 (1P, 1, 48.0), 7.23 (1H, c, J8.0), 7.48 (1H, s). ΕΙΙΔS; π.z = 4′2.4 [M+H]*.

15D: 1-[[1-(Oxiohexvimethyli-7-methoxv-1 H-indol-3-yllcarocnyl]-4-ethy-3-methylpiperazine, hydrochloride satt was prepared using 1-[[1-(cyclchexylmethyl)-7·

methopperazine, hydrochloride satt was prepared using 1-{1-(cyckhexydmethyt)-7-methoxy-1*H*-indol-3-yl]carboryth-3-methylpiperazine. ¹H NMR (400MHz, CD_EOD) & 0.97-1.43 (11H m), 1.56 (2H, br d, J.2.0), 1.64-1.89 (4≒, m), 3.12-3.68 (7H, br m), 3.95 (3H, s), 4.25 (2±, d. J.7.0), 4.5C (2±, br s), 6.77 (1H, d, J.8.0), 7.0 (1H, t, J.8.0), 7.26 (1H, d, J.8.0), 7.5∠ (1H, s). EIMS; m/z = 398.2 'M+H]²

15E: i-[[1-(Cyclohexylmethyl]-7-methoxy-1/Hindol-3-yllca-bonyl]/rens-2.5-dimethyl-4-ethylp.pe-azine, hydrochloride satt

1-{[1-(Cyclohexylme:hy/)-7-methoxy-1*H*-IndoL3-y [carbony] trans-2,5-cime:hybiperazine was prepared following the mathod in example 12, using 1-(cyclohexylmethyl)-7-methoxy-indole-3-carboxylic acid and trans-2,5-dimethyl: perazine. The procedure described under example 14 was used to afford the fills compound. *H NMR (400MHz, CD₂OD) \$4.0.97-1.32 (9H, m), 1.37 (3H, t. J.

30 7.0), 1.44-1.32 (9L, m), 3.12-3.78 (6H, br m), 3.85 (3H, s), 4.17-4.33 (3L, m), 5.00 (1 +, br s), 6.76 (1H, d, J.7.5), 7.10 (1H, 1, J.8.0), 7.21 (1H, d, J.8.0), 7.49 (1+, s). EIMS; m/z = 412.4 {//4+H}.

ISF: 1-[11-(cyclohexylr-ethyli-7-methoxy-* H-indol-3-yl]carbonyll-3.4.5-

itimethylciperazine, hydrochloride salt was prepared using 1-[[1-(cydohexylmethyl)-7-methoxy-1*H*-incol-3-//]carbonyl)-3,5-dirrethylciperazine and iodoir ethane. ¹H NMR (400MHz, CD₂)DD) 5₄ 0.97-. 89 (17H, ir.), 2.96 (3H br si, 3.23-3.48 (4F, br ir.), 3.95

S S

7-methcxy-11-indol-3-ylcenbonyl-3,5-clme.hylpherazine and lodomethane. H NMR trinet rytoperazine. hydroch oride sall was prepared .sing 1-1[14cyclopenlytmethy.)-(1H, d, J7.5), 7.10 (1H, t, J8.0), 7.26 (1H, d, J8.0), 7.60 (1H, s). EIMS; miz = 384.2 (400MHz, CD₃OD) &, 1.23-1.70 (14H, m), 2.40 (1H, hepret, J7.5), 2.96 (3H, br s), 3.2 · · 3.48 (4H, orm), 3.95 (3H, s). 4.36 (2H, d, J.7.0), 4.50 (2H, br d, J 13.5), 6.77 15G: 1-[1-(cyclopent/ime:hyl)-7-methoxy-1H-in-Jol-3-vllcarbcnyl)-3.4.5-

LO.

(3H, s). 4.26 (2H, d, J7.0), 4.49 (2H, br d, J12.0), 8.77 (1H, d, J7.5), 7.10 (1H, t, J

8.0), 7.26 (1H d, J7.5), 7.54 (1H, s). EMS; m/z = 398.0 [M+H]

(400MHz C2₀OD) 84 0.97-1.89 (*44, m), 2.92 (5H, br sj. 3.19-3.61 (5F, br ⊓), 3.95 (3H s), 4.26 (2H, d, J.7.0), 4.43 (2H, m), 6.76 (1H, a, J.7.5), 7.10 (1H, t, J.8.0), 7.27 dinethypiperazine, hydrochlonde salt was prepared using 1-[[1-(cyclonexylmethyi)-7-red nowy-1 H-indol-S-yl carbonyl-8-methy/piperazine and lodomethane, 1H NMR 15H: 1-{[1-(cyc:ohexy/methyl)-7-methoxy-1H-indol-3-yllcarbonyl}-3,4-2

15t: (S-14" - (Cyclopenty/methyl)-7.methoxy-1H-Indol-3-vijcarocnyl)-4-ethyl-3methylpiperazine, hydrochloride sall was prepared using [S]-1-[[1-(1H; d, JB.D). 7.54 (1H, s). EINIS; m/z = 384.2 [M+H]* 5

2.43 (1-1, haptet, J 7.6), 3.12-3.23 (2H, m), 3.47-3.71 (5H, br m), 3.95 (3H, s), 4.38 (2H, d. J.6.9), 4.51 (2H, br.s), 6.77 (1H, d, J.8.2), 7.10 (1H, t, J.7.7), 7.26 (1H, d, J iodoethane. 1H NMR (400MHz, CD₃OD) 8_H * .24** .42 (EH, m), 1.51*1.73 (6H, n), (cyclopantylmethyl)-7-methoxy-1 H-indol-8-yl]carconyll-3-methylpiperezine end

15J: (R)-1-[[1-(Cyclepentylmethyli-7-methexy-1H-indol-3-yl)carbonyl-4-ethyl-3-8.1), 7.60 (1H, s), EIMS, $\pi/z = 384.2 \text{ [M+H]}^{+}$. ន

(c/xlopertylm.elhyl)-7-methoxy-1H-inclol-3-yl]carbonyl}-3-methylp:perazine (precared 35 Setalled in example 12) and icdosthane. HNMR (400 MHz, CD₂OD) S_H 1.24-1.42 (54, brm), 3.35 (3H, s), 4.33 (2H, d, J6.9), 4.51 (2H, br s), 6.77 (1H, 1, J 8.2), 7.10 (84, m), 1.51-1.73 (6H, m), 2.45 (1H, heptet, J.7.6), 3.12-3.23 (2H, m), 3.47-3.71 [1+, 1, J7.7], 7.26 (1H, d, J6.1), 7.60 (1H, s). EIMS; m/z = 984.2 [4/4+]* methylptretezine, hydrochicride salt was prepared using (A)-1-{{1-Ж

2P., d. J7.6), 4.52 (2H, br.d, J14.6), 6.77 (1H, c, J7.9), 7.10 (1H, t. J7.2), 7.27 (1H, 2.43 (* H, heptet, J7.4), 2.86-2 99 (3H, m), 5.17-5.60 (5H, or m), 3.95 (3H, s), 4.38 odomethare. ¹H NMR (400MHz, CD,OD) &, 1.27-1.42 (5H, m), 1.52-1.74 (6H, m), cyclopentylmethyl)-7-methoxy-1 H-indol-3-yllcarbonyl}-3-methylpiperazine and 5K: (S)-1-[[1-(Cyclopentylmethyli-7-methoxy-1h-indol-3-y]garbonyl)-3,4fimelhylpiperazine, hydrochloride salt was prepared us ng (S)-1-(["ä 35

 $d_1 \cup B_1$, 7.63 (14, s). EIMS; m/z = 370.0 [M+H]:

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dmetrytoiperazine, hydrochloride salt was prepared using (*Fi*-1-[]1icyclope 'ty'metry()-7-metroxy-1*H*-indol-3-y(carbony()-3-metry(pi)zerazine and codome:hane. 'H NMR (400MHz, CD₃OD) & 1.27-1.42 (5H, m), 1.52-1.74 (6H, m), 2.43 (1H, hepte:, J.7.4), 2.86-2.99 (3H, m), 3.17-3.60 (5H, br m), 3.95 (3H, s), 4.38 (2H, d, J.7.6), 4.52 (2H, br d, J.14.6), 6.77 (1H, d, J.7.9), 7.10 (1H, t, J.7.7), 7.27 (1H, d, J.8.1), 7.60 (1H, t, J.8.1), 7.80 (1H, t

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13.: [A)-1-[[1-(Cyclopentylmethyl)-7-methoxy-1 H-indol-3-vl]carbonyl-3,4-

15M: 1-{[1:(Cyclonexylmeth/d)-7-methoxy-1 H-indo; 3-yllcarbonyl-3,3-dimethyl-4-ethylolcetazine, hydrochloride salt was prepared using 1-[1-(cyclohexylmethyl)-7-rethoxy-1 H-indol-3-yflcarbonyl)-3,3-dimethylotperazine and iodcethane. 'H NNIR (400Ml-z, CD₃OD) δ_H 0.87-1.90 (20H, m), 2.32-3.69 (6H, ör m), 3.95 (3H, s), 4.22-4.61 (4H, m), Ε.77 (1H, Δ, J.7.9), 7.10 (1H, t, J.8.0), 7.25 (1H, d, J.8.1), 7.53 (*H, s). ΕΙΜS; m/z = 412.4 [M+H**.]

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15N: 1-[1-(Cvckhex/Imethyl)-7-methoxy-1H-incol-3-v|zartonyl]-5.3.415 trimetryloiperazine, hydroxyloride salt was prepared us ng '-[1-(cyclohaxylme:hyl)-7-methoxy-1 H-indol-3-y]carbonyl}-3.3-dimetryloiperazine and iodomethane. 'H NMR (400MHz, CD₃OD) &_H C.98-1.90 (17H, m), 2.86 (3H, s), 3.29-3.70 (4H, m), 3.95 (3H, s), 4.22-4 60 (4H, m), 6.77 (1H, d, J7.7), 7.10 (1H, t, J8.1), 7.25 (1H, d, J8.2), 7.54

(1H, s) E MS; m'z = 398.2 [M+H]*.

20 150: (S)-1-[[1-[c/clohexylneth/h]-nethoxy-1/H-dol-5-v]carborvi-3.4dimethyla perazine trafachlaride sett was prepared ustra /S-1-[1-

dimethylp perazine. Fydrochloide sell was prepared using (*S*)-1-[["- (cyclof exylmethyl)-7-methoxy-". H-indcl-3-yl]carbcnyl}-3-methylploerazine end iodorrethane. ¹H NMR (400I/Hz, CD₃OD) &₁ 0.97-1.89 (14H, m), 2.92 (3F, br ɛ), 3.19-3.6° (5H, br m), 3.95 (3H, s), 4.26 (2H, d, J.7.0), 4.49 (2H, m), 6.76 (1H, d, J. 5.5), 7.10 (1H, t, J.8.0), 7.27 (1H, d. J.8.0), 7.54 (1H, s). ElMS; m/z = 384.2 [M+H]-

15P: (S)-1-[(1-(cyzlohexylnethyl)-7-methoxy-1/Hindol-3-vilcarboxyll-3-methyl-4-(2-fluoroethyl)piperazine, hydrochloride salt was prepared using (S)-1-[(1-(cyzlohexylnethyl)-7-methoxy-1/Hindol-3-yl[carboxyl]-3-methypiperazine and bromo-2-fluoroethare. H NMR (400l/lHz, CD₃OD) 84 0.96-1.90 (14H, m), 3.31 – 30 3.90 (7H, br.m), 3.95 (3H, s), 4.26 (2H, q, J.7.0), 4.40 – 2.59 (2H, m), 4.68 – 5.04 (2H, br.m), 6.77 (1H, d, J.7.5), 7.11 (1H, t, J.8.0), 7.27 (1H, d, J.8.0), 7.56 (1H, s). ElMS; n/z = 416.0 [M+H]*.

Example 16

35 (P-2-III-(Cyclohexylme:hvl)-7-me;hoxy-1*H*-indo-3-ylcarbonyl-cotahydro-2*H*-Eyridol (, 2-alpyraz ne

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8.72 mirof) in dichloromethane (30 ml) were added glycine methy ester hydrochloride (1.09 g. 8.72 mirol), 1-[3-(d methylam no)propyl]-3-ethyl carbodi mide hydrochloride (2.01 g. 10.46 mirol), 1-hydroxybenzotrazole (1.22 g. 9.04 mirol) and triefflylamine (2.42 ml 17.4 mirol). The mixture was stirred under a stream of nitroger for 18 hours. The resulting mixture was weshed with 0.5M hydrox-forc acid (20 ml), wester (2 x 20 ml) and brine (20 ml), driac over sodium sulphate and concertrated to yeld (79.1-(teributoxycarbony))pipendine-2-carboxyglycine methyl ester as a colourless of (2.47 g. 8.23 mirol).

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To a solution of (P)-(-j-1-(tertbutoxycarbonyl)-2-piperidine carboxylic ecio (2.00 g.

(R)-1-(Tertbutoxycarbonyl)plperidine-2-carboxyglycine methyl ester (2.46 g, 8.20 mmol), was dissalved in trilucoacetic acid (10 ml) and the resulting solution stirred for "hour The triflucroace:ic acid was then removed to yield a cotourless oil, which was dissolved in metranol (85 ml) and triethylamine (9.0 ml, 64.6 mmol) acided. The resulting mixture was heated under reflux for 4 hours. The solution was then concentrated to afford a pale orange cill which was recrystallised from heptane 48%, ether 48%, 2-proparol 4%, to yield (R,-cctahydro-1 4-dioxo-2:H-cytido(1,2-alpyrazine 65 white crystals (0.66 g, 3.90 mmo)).

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20 (*f*)-Octahydro-1,4-dioxo-2,4-pyrldo[1,2-a]pyrazine (0.5 g, 2.98 mmol) was added actrionwise to a stirred solution of lithium aluminum hydride (1M in tetrahydrofuran; 11.9 m, 11.3 mmol). The resulting mixture was heated under reflux for C.5 h. The solution was then cooked to 0°C and treated dropwise with water (1.35 ml). 1M soctium hydroxide solution (0.45 ml), then water (1.35 ml). Tetranydrofuran (10 ml) was added and the solution stirred for 0.5 h, before filtration. The filter cake was washed will letrahydrofuran (2 x 5 ml) and the combined filtrate and washings concentrated to yield (*R*)-octahydro-24-pyrldo[1,2-a]pyrazine as a yellow oil (0.29 g, 2.07 mmol).

To a soution of 1-(cyclonexytmethyly-7-methoxy-1/Hindole (0.49 g, 2.35 mmot) in 1,1,2,5-tetrachloroethane (2.5 m), was added oxalyl chloride (0.19 ml, 2.13 mmbl) with stirring under a stream of nitrogen. The mixture was heated at 120°C for 2 hours. After cooling to room temperature, triethylamine (0.30 ml, 2.13 mmbl) was added, followed by (R)-octahydro-2/H-byridol(1.2-a]pyrazine (0.28 g, 2.03 mmol) as a solution in 1,1,2,2-tetrachloroethane (2 ml). The solution was stirred at room temperature for 2 hours. Solium hydroxide solution (1 M; 8 ml) was then acced and the resulting mixture partitioned between clichloromethane (10 ml) and water (10 ml).

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[M+H]

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sulfate and concentrated. The resulting purple oil was purified by flesh chromatography using 38% dichforomethane, 2% methanol as eluent to yield the title product as a pale brown oil (245 mg, 0.60 mmol), [α]₀²² +13° (c 1.87 mg/ml in CHCl₃); ¹H NMR (400M-2, CDCl₃) &₆ 0.92-1.05 (2H, m), 1.12-1.36 (6H, m), 1.48-1.83 (9H, m), 1.83-1.28 (1H, m), 2.37 (1H, ct, J.1.5, 4.0), 2.24 (1H, dt, J.12.0, 3.0), 2.73-2.81 (3H, m), 2.84-2.86 (1H, m), 3.19-3.25 (2H, m), 3.93 (3H, s), 4.18 (2H, d, J.7.0) 4.18-4.32 (2H, m), 6.65 (1H, d, J.7.5), 7.07 (1H, dd, J.8.0, 7.5), 7.25 (1H, s), 7.29 (*H, d, J.8.0) ElMS m/z = 410.2 [M+H]*.

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The organic layer was extracted, washed with water (10 mil), dried over sodium

10 Ехатрle 17

The procedure described under Ξ vample 16 was further used to prepare the following compounds:

17A. (S)-2-[[1-(Cyccobexylmethyl)-7-methoxy-1*Hirclol-3-y*]carbonyl]-octahydro-2Hpyridc[1,2-3|pyrazine, hycrochloride salt was prepared using (S)-(·)-1-(tertbutoxy-carbonyl)-2-piparidire carboxylic acid. [α]₂²² -18 (free base; c 4.05 rrg/ml in CHCl₃); ¹H NMR (4C0MHz, CDCl₃), δ₁-0.99-1.C8 (2H, m), 1.13-1.28 (3H, m), -.50-2.03 (12H, m), 3.02-3.12 (1H, rr), 3.13-3.20 (3H, m), 3.43-3.50 (3H, m), 3.95 (3H, s), 4.27 (2H, d, J.7.0), 4.49-4.59 (2H, m), 6.77 (1H, d, J.7.5), 7.11 (1H, dd, J.8.0, 7.5), 7.27 (1H, d, J.8.0, 7.5), 7.27 (1H, d, J.8.0), 7.54 (1H, s); EIMS: rr/z = 410.5 [M4.H].

17B. (R)-2-(i1-(Cydo)asylmathyl)-7-methaxy-1*H*-indo-3-ylearbonyl)-oclahydro-2*H*
Pyrrolo[1.2-alpyrazing was prepared using (*R*)-(+)-1-(tertbutoxycarbonyl)-2
Fyrroliding carboxylic acid. ¹H N/AR (400M/-z, CDCl₃) &₁ 0.92-1.04 (2+, m), 1.13-1.21 (3H, m), 1.40-1.45 (** F, m), 1.57-1.89 (5H, m), 2.00-2.1C (1H, m), 2.15-2.29 (2H, m), 2.76-2.85 (1H, m), 3.02-3.23 (3H, m), 3.93 (3H, s), 4.18 (2H, d, J.7.C), 2.32-4.56 (2H, m), 5.57 (1H, d, J.7.O), 7.09 (1H, t, J.8.C), 7.25-7.30 (2H m); EMS: m/z = 396.2 (M+-1)*

17C. (S:-2-{f.-(Cyclohexylmethyl)-7-methoxy-1H4ndol-3-ylkcarbonyl)-cctahyd-o-2H-Pytrolof1.2-abytrazhe. hydrochlofde sall was prepared using (S)-(+)-1.

20 (terttutoxycarbonyl)-2-pytrolidine carboxylic acid. ¹H NN/R of free base (400N/Hz, CECle) 54, 0.53-1.63 (2H, m), 1.11-1.21 (3H, m), 1.35-1.46 (1H, m), 1.56-1.89 (9H m), 1.95-2.05 (1+, m), 2.21-2.27 (2H, m), 2.77 (1H, t, J.11.0), 8.07 (1H, d. J.10.5), 3.36-3.2C (2H, m), 3.93 (3H, s), 4.18 (2H, d, J7.0), 4.26-4.41 (1H, m), 2.43-4.56 (1H, m), 6.65 (1H, d. J.8.0), 7.07 (1H, t, J.6.0), 7.25-7.30 (2H, m); ElMS: m/z = 396.2

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17E: (S.2-(i'-(Cyclopentylnethyl)-7-methoxy-1,4-indal-3-yllcarbonyl)-octahyoro-2H-pymolo 1 2-alpyyezine, hydrochloride salt was prepared using (S)-(·)-1-

10 (terbutoxycarbonyt)-2-pyrrolidine carboxylic acid and 1-tcyclopentythrethyll-7-methoxy-1/+ndole. ¹-i-NMR (400M-1z, CDClg) 8_{th} 1.21-2.23 (15H, m), 2.41 (1H, heptet, J7.5), 2.75 (1H, t, J11.0), 3.01-3.20 (5H, m), 3.94 (3-1, s), 4.30 (2H, d, J7.5), 7.07 (1H, t, J7.5), 7.23-7.21 (2H, m). ElMS; mz = 362.2 [M--1].

15 17E: (3R,9R)-2-[(1-(Cyclohexylmethyl)-7-rrethoxy-1H-inocl-3-yllcarbonyl)-3-isobutyloctahydro-2H-pyrrolof1,2-alpyrazina was prepared using (3R,9R)-oclahydro-1,4-dioxo-2H-pyrrolof1,2-alpyrazina (commercially available) instead of (R)-oclahydro-1,4-dioxo-2H-pyridof1,2-alpyrazine. EIMS; mz = 452.2 [M-1]*.
17G: (3S,9S)-2-([1-(Cyclohexylmethyl)-7-methoxy-1H-inool-3-yllcarbonyl)-3-

20 <u>reflytoctahydro-2*H-*pyrrolof1,2-€pyrazine</u> was prepared using 1-(tertbu:oxycarbonyl)prolire and t-alanine methyl ester hydrochloride salt. EIMS; m/z = 410.0 [M+H]*.

17H: (2R,cs)-1-ff1-(Cyclohexymethyl-7-methoxy-1/H-indol-3-yl carbonyl-2-fohydroxylerhyl-4-methylolperazine was prepared using 1-methyl-1-25 (terticutoxycarbonyl)glysine and 3-threonine methyl ester hydrochloride salt. EMS: mz = 414.2 [M+H]*.

171: (2.5.c.R)-1-{[1-{Oxlorex/Imethyl}-7-methoxy-1H-indol-3-yl]carbonyl}-2-{c_-}
hydroxylethyl-4-methylpiperazing was prepared using 1-methyl-1(tartbutoxycarbonyl)glycine and L-:hreonine methyl ester hydrochlorice salt. EIMS:

3.3 m/z = 414.2 [M+H]*.

17.J. (S)-2-[[1-(Cyclohexyknethyl)-7-mathoxy-1/H-indol-3-yl carboryll-3.3-clme:hyl-cyclohydro-2/H-pyrrolo[1,2-alpyrazine was prepared using 1-(terrbutoxycarbonyl)-proline and arrincisobutyric acid methyl ester hydrochloride sait. EIMS; m/z = 424.2

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Example 18

A

-{[1-{Cvdohexvlmethvl}-7-methavy-1H-Evdo-3-{ficerbory/}-3-{fl.zcomethvl}

<u>picerazire, hydrochloride sali</u>

mix.ure was hæted to 80°C for 16 h, filteren and the precipitate washed with toluene (35.87 g, 149.2 mmol) and trie:hylamine (37 ml, 269 mmol) in toluene (75 ml). The magnesium sulfate and evaporated to afforc 1,4-dibenzyl-p.perazine-2-carboxylic (200 ml). The combined filtrates were washed with water (2 x 200 ml), dried with To a solution of 2,3-dib omopropionic acid ethyl ester (21.91 ml, 150.7 mmol) in tolusne (175 ml) at 40°C was added a mixture of N.N-ditenzylethylenediamine aclc ethyl ester (45.57 g) as an orange oil. S 2

ethyl ester (10g, 32.1 mmol) in tetra-ryclocfuran (30 ml) and stirred for 16 hours. The m xture was quenched by slow addition of sodium hydroxide solution i4 M, 150 ml), Lithium aluminium hydride (1 M solution in tetrahydrofuran, 32 ml, 32 mmol) at 0°C nas treeted orcpwise with a sclution of 1,4-dibenzyl-piperazine-2-carboxylic acid

followed by dichloromethene (200 ml). The organic phase was separated, dried with sodium su fate and evaporated to afford 1,4-dibenzy-2-(nycicxymethyl)piperazine (8.36 g), as an crange oil. 찬

To a solutior of diethylaminosuliur trifluoride (1.5 ml, 12.16 mmol) ir dichlorome:hane

mmol) in dich oromethans (20 ml) over 10 minutes. The mixture was stirred for 16 h (10 mi) at -72°C was added 1,4-d.benzyl-2-(hydroxymethy piperazine (3 g. 10.1 밁

separeted. The aqueous phase was extracted with clichloromethane (2 x 30 ml) and he corrbined organic layers dried with sodium sulfate and evaporated. The residue was purified or flash chromatograpy eluting with 20% (w/v) ethyl acetate in hexane whilst warming to room temperature and treated with water (20 ml). The aqueous phase was basitied to ph. 9 using 4 IV sodium hyperoxide and the organic ohase 23

o a stury of pelladium on carbon (10% w/wl, 1.g), in ethanol (20 ml) was added 1,4mixrure was heeted to 65°C under an hydrogen atmosphere (5 etm.) 'o' 72 hours to afford 1,4-dibenzyt-2-(fluoromethyl)piperazine (0.94 g) as a colcurless oil dicenzy!-2-(fluoromethyt)piperazine (2.58 g, 10 mmol) in ethanol (20 ml).

olmethylami nopropyi)-3-ethylcarbodiimide hydrochbride (0.47 g, 2.45 mmol) and 1were evaporated to afford 2-(fluorcmethy];piperaz ne (0.97 g) as a colourless solld, filtered through dicalite and the dicalite washed with ethanof (50 ml). The fittrates o a solution of 1-(cyclohexylimethyl-7-methoxy-ndole-3-carboxylic acid (0.59 g. 2.04 ாயல், p ஒpered following the method in Example 1) and 2-(fluoromethy/) ploerazine (0 37 g, 3.15 mmol) in cichloromethane (15 ml) was added 1-(9-8 છ

hydroxy benzotriazo'e (0.07 g, 0.51 mmol). The mixture was stirred at room

emperature for 18 h and evaporated. The residue was purified by flash

title comparent (free base) as a colourless oil (0.47 g). The free base (0.05 g) was dissolved in dielhyl ether (3 ml) and treated dropwitse with 2 M hydroch onic acid in dielfryl ether (1 ml). The resulting precipitate was collected by filtration, washed with dielfryl ether (10 ml) and dried under reduced pressure to afford the title compound (1:1 hydrochloric acid sall; as a colour ess solid (0.05 g, 0.12 mrol). 14 NMR (400MHz, CD₃OD) 54, C.98-1.27 (5H, m), 1.57 (2H, br c., J.12.9), 1.63-1.90 (4H, m). 3.21-3.33 (4H, m), 3.68-3.78 (1H, m), 3.35 (3H, si, 4.26 (2H, d. J.7.1), 4.43-4.82 (4H, m), 8.77 (1H, d. J.7.5), 7.27 (1H, d. J.8.0), 7.57 (1H, s); Ell/IS: m/z 270.2 (Fragment+H)².

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chromatography eluting with 0-10 % (v/v) methanol in dichic mmethane to afford the

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Example 19

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1-{[1-:'Cyclo'rexylmethyli-Z-methoxy-1/Hindol-3-yl'carbonyll-3-(fl.oromethyl)-4-cyclopropyl piperazine, hydrochlor de salt

To a solution of 1-{1-(Oyclohexylmethyl)-7-methoxy-1-f-indol-3-yllcarbcnyl}-3-(fluoromethyl) piperaz ne (0.2 g, 0.52 mmol, prepared folicwing the method in Example 18) in methanol (10 mf, was added acetic add (C.18 ml, 3.1 mmol), 4Å molecular sieves (1 g), [(1-ethoxycyclopropyl)axy] trimethylsilane (0.62 ml, 3.1 mmol) and sodium cyanaborohydride (0.15 g, 2.33 mmol). The mixture was heated to 70°C

for 18 h, iffered and the precipitate washed with dichloromethane (20 ml) and methanol (20 ml). The fittates were evaporated, dissolved in dichloromethane (30 ml) and washed with sodium hydroxide solution (4 M, 15 ml) and saturated sodium choride solution (15 ml). The organic phase was dried with sodium sulfate, evaporated and the residue purified by flash chromatography eluting with 2 % (v/v)

25 methanol in dichloromethane to afford the title compound ifree base) as a yellow oil (3.2 g). The free base was dissolved ir diethyl ether (3 rd) and treated chopwise with 2 M hydrochloric acid in diethyl ether (1 ml). The resulting pracipitate was collected by filtration, washed with diethyl ether (10 ml) and dried under reduced pressure to afford the title compound (1:1 hydrochloric acid sell) as a colourless solid (0.2 g, 0.43 or mmd). High (400MHz, CD₅OD) S₁ 0.91-1.25 (9H, m), 1.57 (2H, brid, J12.6), 1.62-1.81 (4H, m), 2.8-2.93 (1H, rr), 3.33-3.82 (5H, m), 3.56 (3H s), 4.27 (2H, d, J7.3), 7.11 (1H, t, J.9.1).

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7.26 (1H, & J.8.1); 7.56 (1H, s); EIMS: m/z 428.2 [M+H]*

Example 20

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in-vitro determination of efficacy and potency at the human CB1 receptor expressed in CHO cells

5 Chinese Hamster Ovary (CHO) cells expressing the human CB1 receptor and a luciforase reporter gene were suspended in phenol red / sarum tree DMEM / F-12 rut mix containing perfellin / streptomycin (50U/50 µg/ml) and fungizore (1 µg/ml) and seeded into 95 well plates at a density of 3 x 10° cells per well (100 µl final volume). Cells were incubated overnight (approx. 18 h et 37°C, 5% 00z/95% air) prior to assay.

The test compound (10mM solution in DNSO) was siluted in F12 ML1 Mix to give a range of stack solutions from 0.11 mM to 0.11 mM. The stock solutions (10µ) were added directly to the relevant wells. The plates were incutated at 37°C for 5 hours to allow agonist-induced expression of the luciferase enzyme. Under subdued light, Luc_ite substrate (Packard; reconstituted as per manufacturer's instructions; 100 µl) was added to each well. Plates were covered with Top Seal and then incubated at room temperature for 5 mirutes before counting on the Packerd TopCount (single photon counting, 0.01 mirute count time, 5 minute count delay).

A 'best-fit' curve was fitted by a minimum sum of squares method to the plot of counts per second (CPS) against compound concentration (M) to obtain an EC₃₀ value. Table 1 shows the pEC₃₀ values obtained for some representative compouncs of the invention.

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1-[[1-(Cyclopentylmethyl;-7-methcxy-1+- indol-3-yl]carbonyl;-4-ethylpiperazine, hydrochloride sait hydrochloride sait 1-[[1-(Cyclor-exylmethyl]:-7-methcxy-1+- indol-3-yl]carbonyl]-4-(2-hydroxy- ethyl)piperazine, trifluoroacetic acid salt 58[[1-(Cyclor-bayylmethyl,-7-fluoro-1+- indol-3-yl-sarbonyl,-4-ethylmerazine		PEC
	ر م ا + L-Axor	6.5
	Zine,	
	; }-	
	3xy-17-	9.9
	•	
	id salt	
indol-3-vil:serconv.>-4-ethvininera	3H:	7.0
hydrocaloride sail	\$ \$ -	

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1.7	- -	2 ci	ය ග	0 6	7.5	7.6	7.9	7.6	7.5
3	* O	E C	9.00		4				
(+)-1-[[1-(1-Cyckhexyleihyl)-1H-indol-3- yilearboryi]-4-eifyipiparazine,	hydrochloride salk	1-{ 1-;Oyctonex-3-enylmethydi-7- metroxy-1.H-indol-3-y carbony -4- ethy‡iperazine	1-{[1-(Cyclonexylmethyl)-6-fluoro-1.H-incloh3-yl]carbony}-4-methylpiperazine, hydrochlorice salt	1-{[1-{Oyclonexylmethyl}.7-methoxy-1H-incol-3-yl]cartony]-3,5-dimethyl-4-ethyt: perazine, hydrochloride salt	[[1-icyclohexylmethyt]-7-methoxy-1 <i>H</i> -incol-3-yt]:ærbonyt]-3,4,5- trimethylpiperazine, hydrochloriae salt	(S)-1-(1-(cyclohezylinethyi)-7-methoxy-1-H-ndol-3-yi ca-bonyii-3,4-dimethyipperaz ne, hydrochloride set:	(S)-2-(11-(Cyc ohexylme:hyl)-7-me:hoxy-1-H-indol-3-yl)ca:bonyl;-octahydro-2-H-pyrido-[1.2-a]pyrazine, hydrochloride salt	(S)-2-([1-(Cyc ohexylme:hyl)-7-me:hoxy-1 <i>H</i> -indok-3-yljca bonyl;-octahydro-2 <i>H</i> pyrrclo-[1, 2-a]pyrazine, hyd:ochlorice salt	(S)-2-[[1-(Cyclopentylmethylt-7-methoxy-1H-indol-3-y][carbony/,-octahydro-2H-pyrldc-[1, 2-a][cyrazine, hydrochloride salt
IS-(+)			डा	· •	.57	150	17A	170	170

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Example 21: Tall Flick Latency in Mice

Mice were trained to sit still in a tail flick apparatus (Ugc Bas ia, Italy) whilst tail flick latency was measured. The tail was exposed to a focused beam of rediant heat at a 5 point approximately 2.5 cm from the tip. Tail flick latency was defined as the interval between the appliance of the thermal stimulus and withcrawal of the tail. A 12 second cut-off was employed to prevent tissue damage. Four groups of eight mice were treated with vehicle or one of three doses of the test compound, administered intravencusly (vehicle: saline 9 gilt, Injection volume 10 mt/kg). Tail flick latency was measured before administration of the test compound administration. The ED₃, was calculated at T_{max}.

The compounds of examples 14, 15F, 15O, 17A, 17C, and 17D significantly increased the tail flick latency with an ED $_{\rm DS}$ < 5 μ mot/kg.